Daratumumab, Carfilzomib, Lenalidomide and Dexamethasone (Dara-KRd), Autologous Transplantation and MRD Response-Adapted Treatment Duration and Cessation in Newly Diagnosed Multiple Myeloma (NDMM)

MASTER trial

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18th International Myeloma Workshop, Vienna 2021

Disclosures

- Research support: Amgen, Janssen, BMS, AbbVie, Ionis, Genentech
- Honorarium: Amgen, Janssen, Sanofi, Karyopharm, BMS, Astra Zeneca

Background

- Daratumumab when added to PI, IMiD or PI+ IMiD combinations increases the depth and duration of responses in NDMM, including patients treated with AHCT.
- While responses are heterogeneous, treatments are typically developed without accounting for kinetics or depth of response.
- MRD is prognostic, but response-adapted therapy to achieve MRD (-) status has not been formally tested.
- Natural history of patients with confirmed MRD (-) responses managed without maintenance has not been described.

Attal M et al. N Engl J Med 2017 376:1311; Mateos MV et al. N Engl J Med 2018, 376:518; Moreau P et al. Lancet 2019, 394:29; Facon T et al. N Engl J Med 2019, 380:2104; Voorhes P et al. Blood 2020, 136:936; Jasielec JK et al. Blood 2020, 136:2513

Objectives

Primary

- To determine the rate of MRD(-) responses ($<10^{-5}$) utilizing NGS (clonoSEQ®)in patients treated with Dara-KRd induction, AHCT, and MRD-based response-adapted Dara-KRd consolidation.

Key Secondary

- Determine the toxicity of Dara-KRd
- Determine conventional IMWG response
- Outcomes of observation without maintenance upon confirmed MRD (-)

Exploratory

- Determine MRD (-) rates by NGS with threshold of 10^{-6}

MRD tested on ”first pull” and reported utilizing <u>intent-to-treat</u> principle according to International Harmonization

Costa LJ et al Leukemia 2021 35:18

Key Eligibility

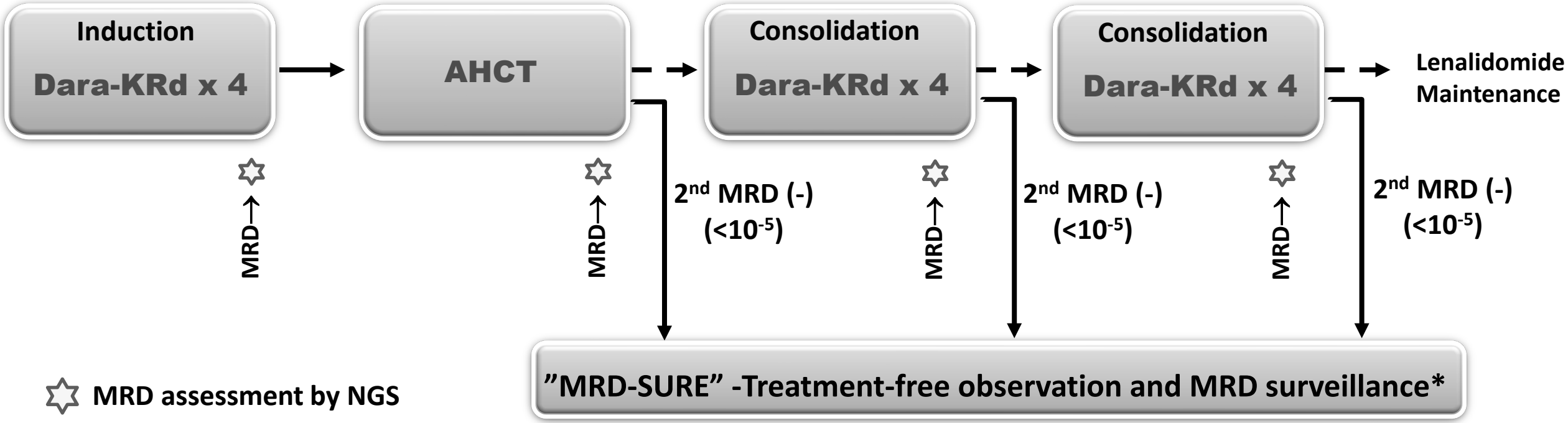
- NDMM with measurable disease
- Untreated (up to 1 cycle of VCD allowed)
- No age limit
- ECOG 0-2
- CrCl $\geq$ 40 ml/min
- No significant cardiopulmonary disease, concomitant or recent malignancy

Planned Enrichment for MM with High-Risk Cytogenetic Abnormalities

Treatment

Dara-KRd

- Daratumumab 16 mg/m^2 days 1,8,15,22 (days 1,15 C 3-6; day 1 C >6)
- Carfilzomib (20) 56 mg/m^2 Days 1,8,15
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40mg PO Days 1,8,15,22



*24 and 72 weeks after completion of therapy

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Patients

- 123 patients enrolled
- 118 (96%) with MRD trackable by ClonoSEQ®
- Median follow-up of 23.8 months

Characteristic		Standard-risk 0 HRCA N=53 (43%)	High-risk 1 HRCA N=46 (37%)	Ultra high-risk 2+ HRCA N=24 (20%)	Total N=123
Gender					
	Male	33 (62%)	24 (52%)	13 (54%)	70 (57%)
	Female	20 (38%)	22 (48%)	11 (46%)	53 (43%)
Age					
	Median (range)	60 (36-79)	61 (35-77)	60 (41-72)	60 (35-79)
	Age ≥ 70	12 (23%)	10 (22%)	2 (8%)	24 (20%)
Race/ethnicity					
	Whites	42 (79%)	33 (72%)	19 (79%)	94 (76%)
	Racial/ethnic minorities	11 (21%)	13 (28%)	5(21%)	29 (23%)
ECOG					
	0-1	42 (79%)	40 (87%)	17 (71%)	99 (80%)
	2	11 (21%)	6 (13%)	7 (29%)	24 (20%)

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

Patients (cont)

Characteristic	Standard-risk 0 HRCA N=53 (43%)	High-risk 1 HRCA N=46 (37%)	Ultra high-risk 2+ HRCA N=24 (20%)	Total N=123
LDH				
<ULN	45 (85%)	34 (74%)	18 (75%)	97 (79%)
≥ ULN	8 (15%)	12 (26%)	6 (25%)	26 (21%)
Cytogenetic abnormality				
hyperdiploidy	27 (51%)	20 (44%)	4 (17%)	51 (41%)
del(13q)	19 (36%)	20 (44%)	18 (75%)	57 (46%)
gain/amplification 1q	0 (0%)	24(52%)	20 (83%)	44 (36%)
del(1p)	3 (6%)	4 (9%)	5 (21%)	12 (10%)
t(11;14)	14 (26%)	7 (15%)	0 (0%)	21 (17%)
t(4;14)	0 (0%)	8 (17%)	13 (54%)	21 (17%)
t(14;16)	0 (0%)	2 (4%)	4 (17%)	6 (5%)
del(17p)	0 (0%)	12 (26%)	14 (58%)	26 (21%)
R-ISS				
1	25 (47%)	11 (24%)	0 (0%)	35 (28%)
2	27 (51%)	23 (50%)	13 (54%)	63 (51%)
3	1 (2%)	12 (26%)	11 (46%)	25 (20%)

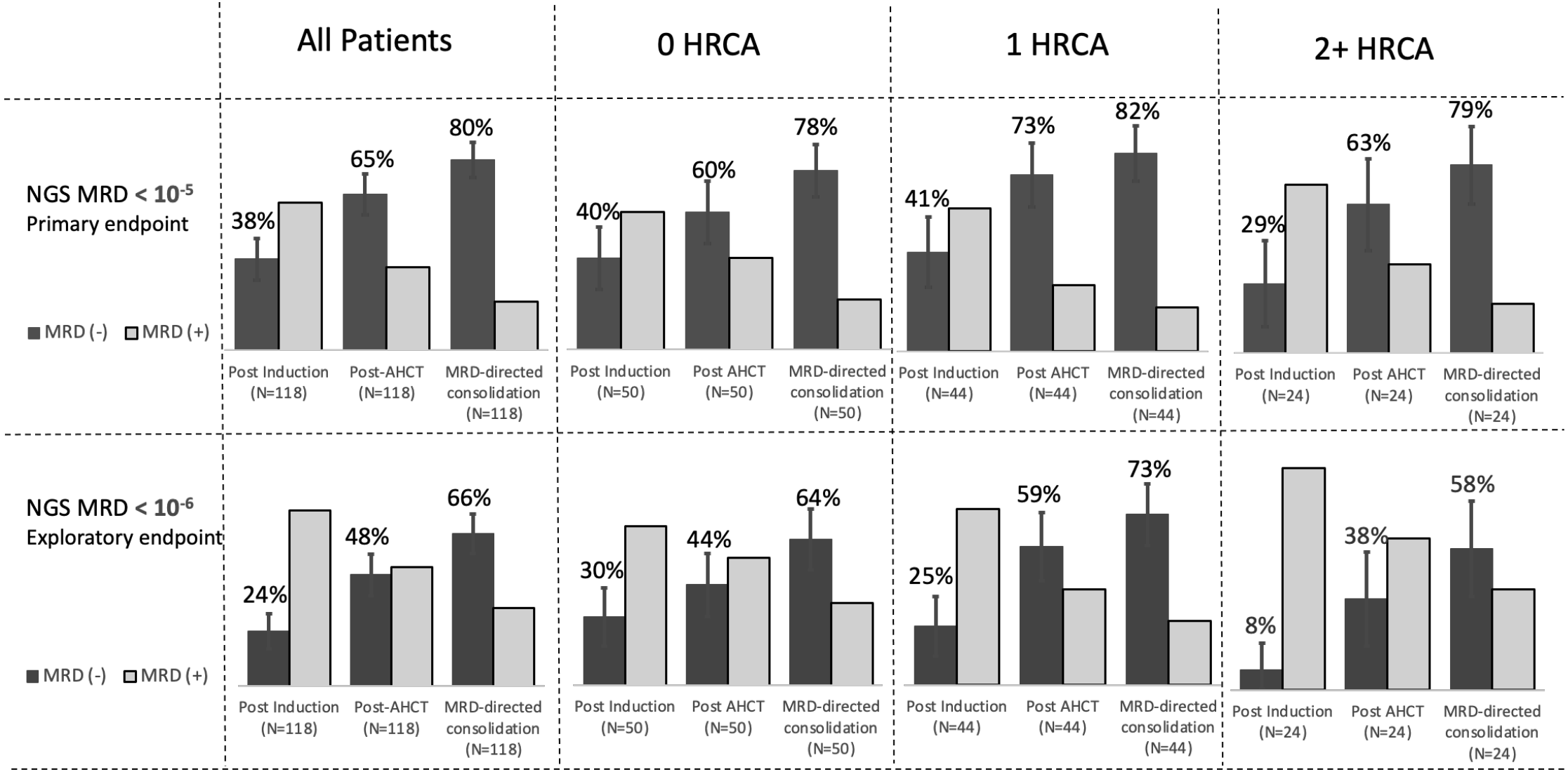
HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

Safety

Adverse Event	Any Grade	Grade ≥ 3
	No. of patients (%)	
Any	123 (100)	91 (74)
Hematologic		
Neutropenia	51 (41)	43 (35)
Lymphopenia	34 (28)	27 (22)
Anemia	26 (21)	13 (11)
Thrombocytopenia	24 (20)	10 (8)
Leukopenia	22 (18)	12 (10)
Non-Hematologic		
Fatigue	68 (55)	11 (9)
Bone pain	68 (55)	7 (6)
Rash maculo-papular	50 (41)	5 (4)
Nausea	49 (40)	0
Constipation	48 (39)	0
Upper Respiratory Infection	45 (37)	1 (1)
Diarrhea	43 (35)	5 (4)
Insomnia	35 (28)	3 (2)
Infusion related reaction	34 (28)	2 (2)
Dyspnea	34 (28)	2 (2)
Cough	32 (26)	0
Hypertension	32 (26)	12 (10)
Dizziness	30 (24)	1 (1)
Peripheral sensory neuropathy	26 (21)	2 (2)

- 25 TE-SAEs
  - Pneumonia (N=8)
  - Pulmonary embolism (N=3)
  - Fever and neutropenia (N=2)
  - aHUS (N=1)
  - IRR (N=1)
  - Atrial fibrillation (N=1)
  - Other (N=9)
- 3 deaths
  - Unwitnessed sudden death on second week of induction
  - Metapneumovirus pneumonia 9 days after AHCT
  - Unwitnessed sudden death 2 months after AHCT

Best MRD response by phase of therapy



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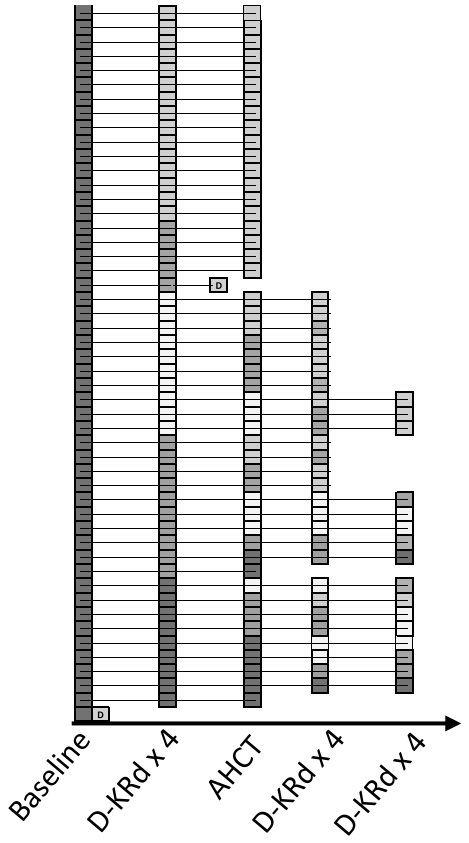
MRD level by phase of therapy

0 HRCA

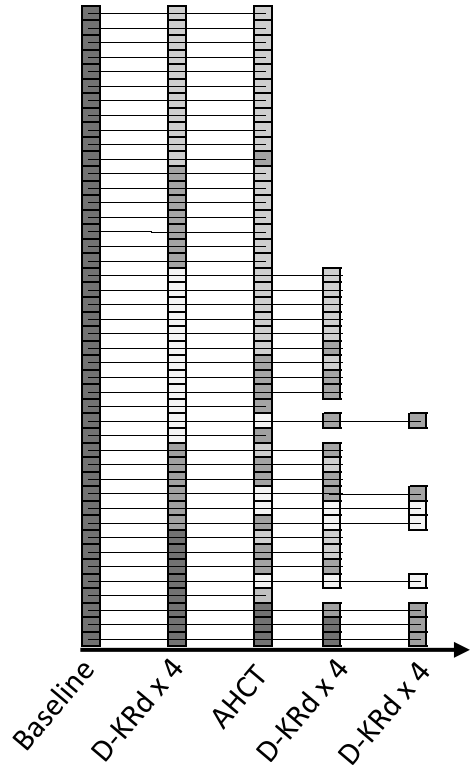


62% confirmed $<10^{-5}$

⇩

Treatment cessation

1 HRCA



78% confirmed $<10^{-5}$

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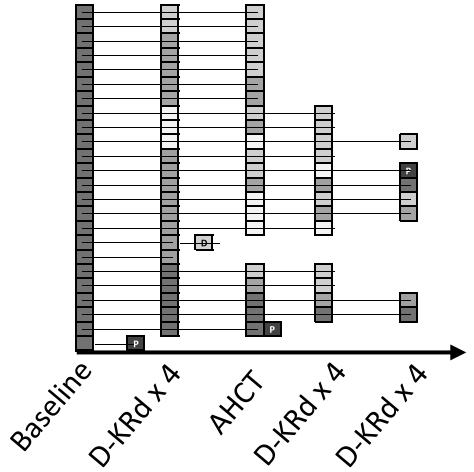
Treatment cessation

2+ HRCA



63% confirmed $<10^{-5}$

⇩

Treatment cessation

- $>10^{-3}$
- 10^{-3} to 10^{-4}
- 10^{-4} to 10^{-5}
- 10^{-5} to 10^{-6}
- $<10^{-6}$
- D Death
- P Progression

HRCA = gain/amp 1q, t(4;14), t(14;16), t(14;20) or del(17p)

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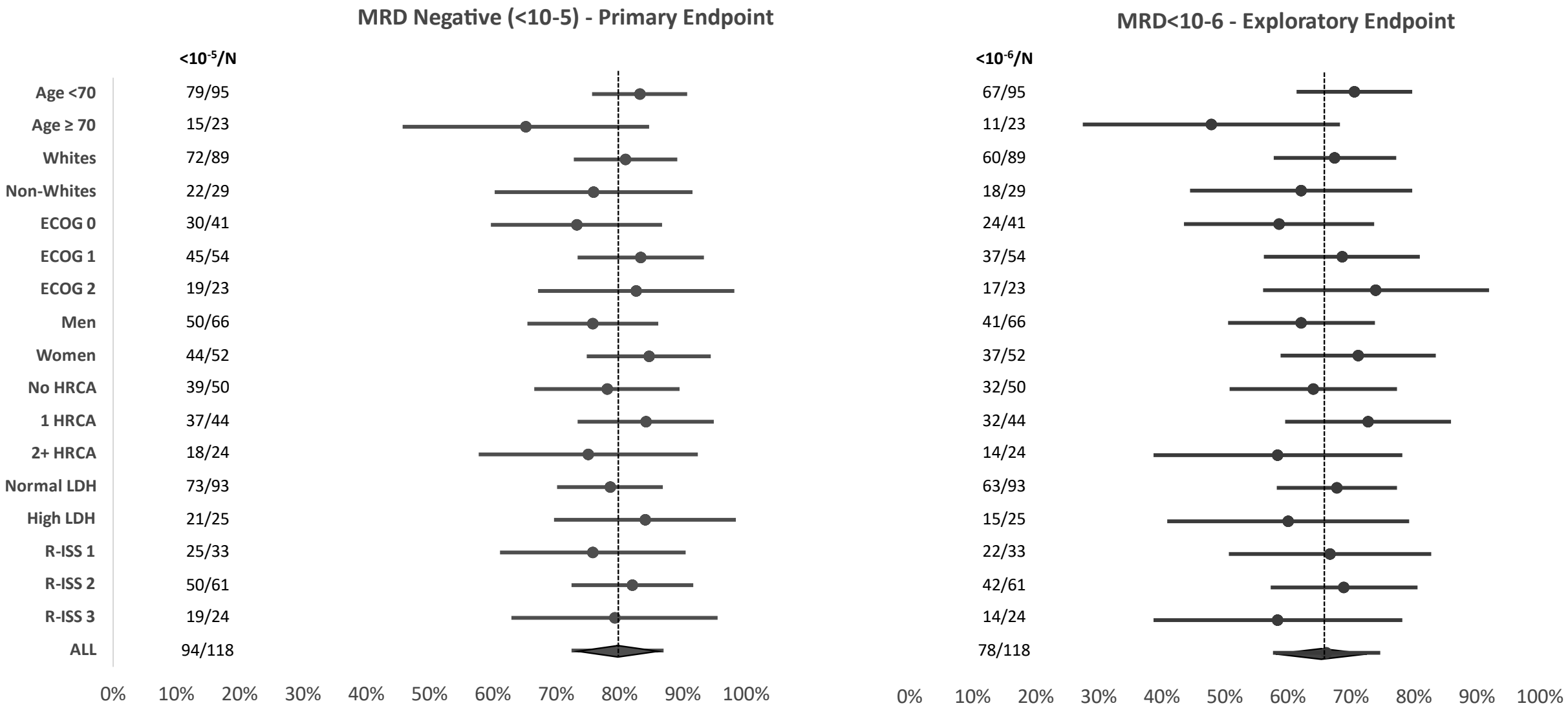
MRD response by subset



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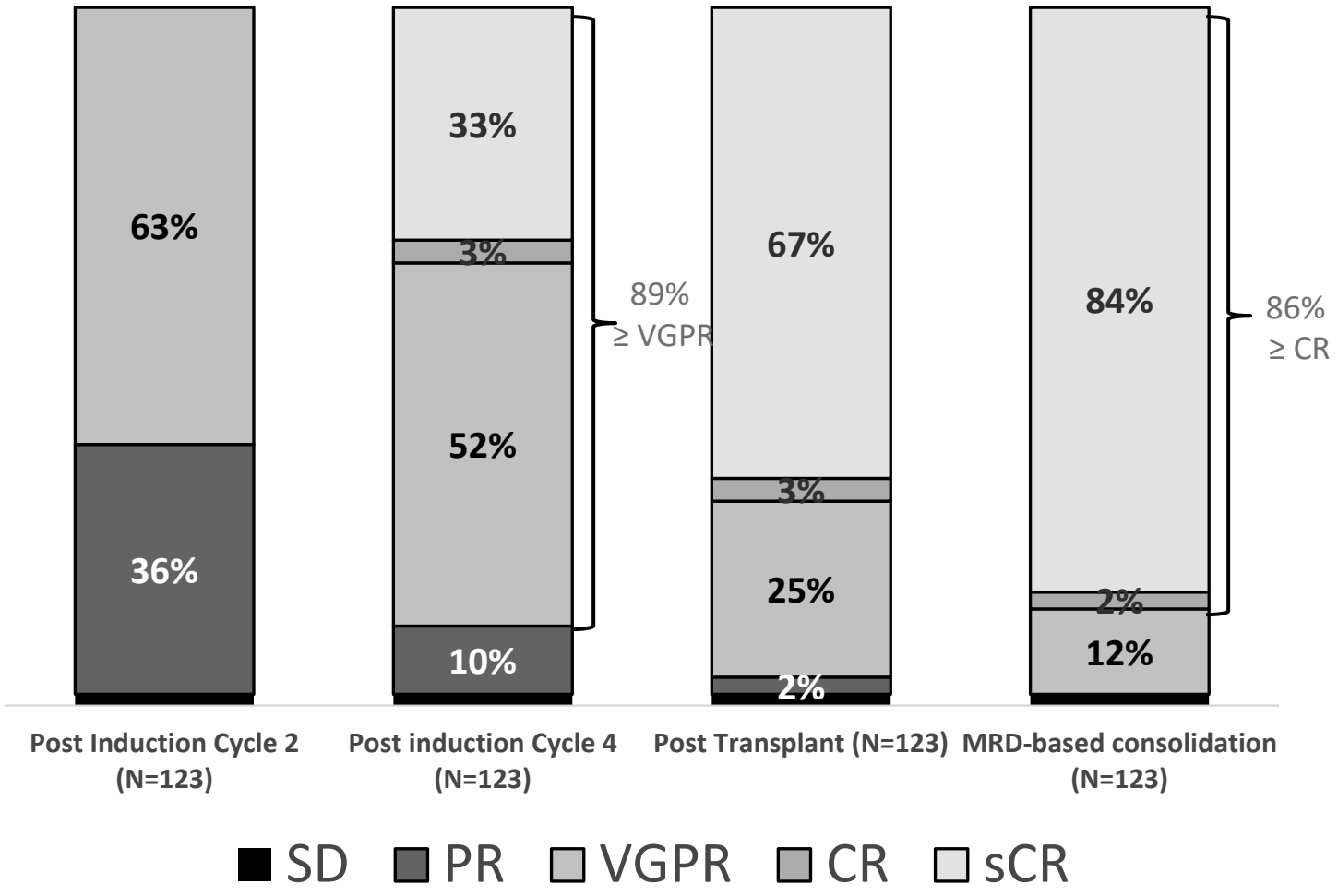
Best IMWG response by phase of therapy



- 6 progressions during therapy
  - 1 during induction,
  - 1 after AHCT
  - 4 on consolidation
- All with gain/amp of 1q
- 5/6 had 2+ HRCA

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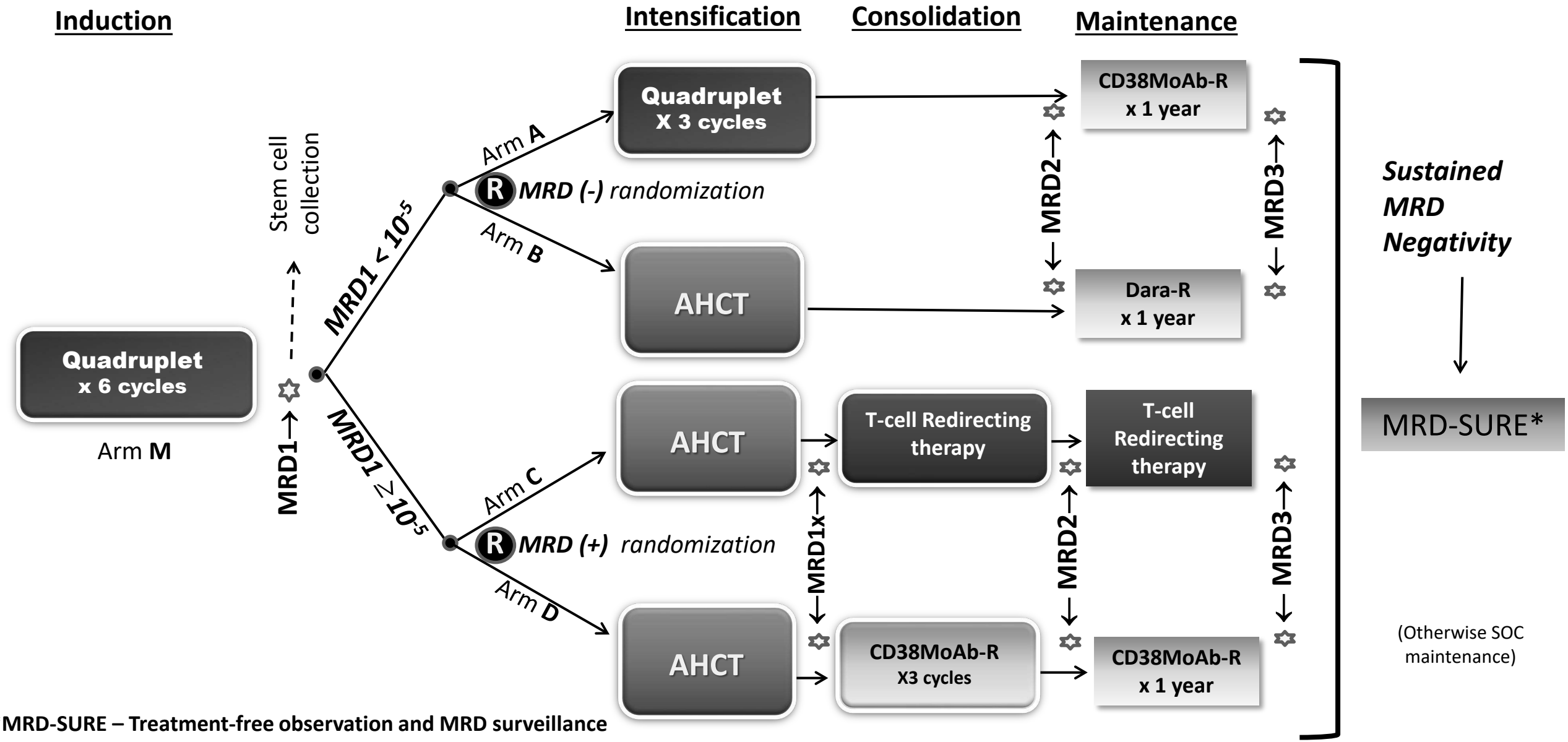
Conclusions

- NGS MRD-based, response adapted therapy is feasible in ~96% of patients in multi center setting.
- Dara-KRd is a safe regimen with rapid responses and unprecedented rates of MRD negativity in NDMM achievable across the risk spectrum
- Quadruplet therapy and achievement of confirmed MRD (-) CR enables the exploration of treatment cessation and “MRD-SURE” as alternative to continuous therapy.
- Novel consolidative strategies need to be explored in ultra high-risk patients with suboptimal clearance of MRD on quadruplet therapy

Long term follow up will inform the risk of progression and MRD resurgence during MRD-SURE

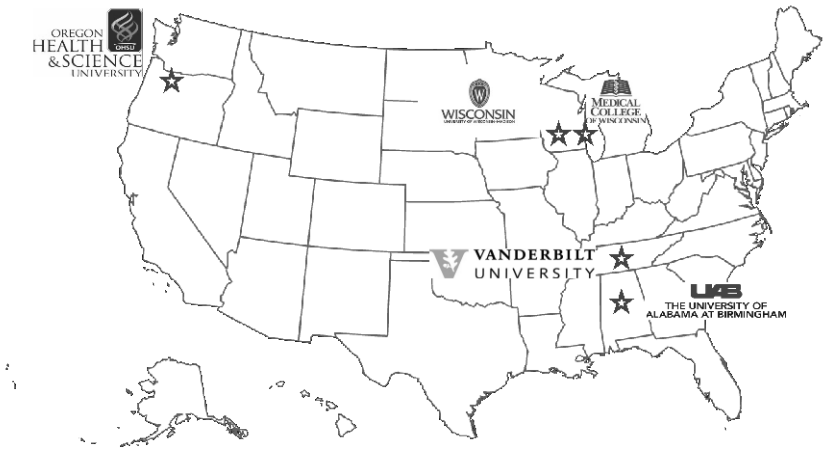
Future



*MRD-SURE – Treatment-free observation and MRD surveillance

Acknowledgements

- Patients and their families.
- Performed by Academic Consortium to Overcome Multiple Myeloma through Innovative Trials (COMMIT)
- James Omel and Yelak Biru
- Investigator-initiated trial, support from Amgen and Janssen.
- Adaptive Biotechnologies for partnership and assistance with IDE



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